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**Modification of hematopoietic stem/progenitor cells with CD19-specific chimeric antigen receptors as a novel approach for cancer immunotherapy.**

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**Public Summary:**

We propose a gene therapy to hematopoietic stem/progenitor cells (HSPC) as a novel approach to consistently produce immune cells that can target and kill malignant leukemia and lymphoma cancer cells.

**Scientific Abstract:**

Chimeric antigen receptors (CARs) against CD19 have been shown to direct T-cells to specifically target B-lineage malignant cells in animal models and clinical trials, with efficient tumor cell lysis. However, in some cases, there has been insufficient persistence of effector cells, limiting clinical efficacy. We propose gene transfer to hematopoietic stem/progenitor cells (HSPC) as a novel approach to deliver the CD19-specific CAR, with potential for ensuring persistent production of effector cells of multiple lineages targeting B-lineage malignant cells. Assessments were performed using in vitro myeloid or natural killer (NK) cell differentiation of human HSPCs transduced with lentiviral vectors carrying first and second generations of CD19-specific CAR. Gene transfer did not impair hematopoietic differentiation and cell proliferation when transduced at 1-2 copies/cell. CAR-bearing myeloid and NK cells specifically lysed CD19-positive cells, with second-generation CAR including CD28 domains being more efficient in NK cells. Our results provide evidence for the feasibility and efficacy of the modification of HSPC with CAR as a strategy for generating multiple lineages of effector cells for immunotherapy against B-lineage malignancies to augment graft-versus-leukemia activity.

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